



**BOX PATENT**

Attorney Docket No. 24460

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

In re Application of:

BECKER et al.

Serial No.: 09/718,425

Art Unit: 1634

Filed: November 24, 2000

Examiner: TAYLOR, JANELL E.

For: **METHOD AND SYSTEM FOR PREDICTING AMINO ACID SEQUENCES  
COMPATIBLE WITH A SPECIFIED THREE DIMENSIONAL STRUCTURE**

**Appendix A**

Please amend claim 1 and add new claim 23 as outlined in the following "marked up" copy of the claims.

1. (Amended) A computer-implemented method for predicting at least one amino acid sequence compatible with a specified three-dimensional (3D) structure of a protein or peptide; which method comprises the steps of:
  - a. providing a coordinate set representing the backbone of said 3D structure;
  - b. constructing a reduced virtual representation for the 3D structure provide in step (a);
  - c. determining for each position along the virtual structure representation provided in step (b) its solvent accessibility;
  - d. constructing an initial amino acid sequence by randomly assigning for each position along the structure an amino acid residue selected randomly from a predefined group

of amino acids having a solvent accessibility compatible with the solvent accessibility of said position;

- e. randomly selecting one or more positions along the sequence provided in step (d) and applying on each position a Monte-Carlo simulation in sequence space and rotamer space, said simulation comprising one or more scoring function calculating steps which include:
  - i. randomly selecting one or more amino acid residues of the same solvent accessibility as that defined for said position to obtain a mutation;
  - ii. calculating an energy scoring function for each possible rotamer of each amino acid residue provided in step (i) based on their said reduced virtual representation;
  - iii. selecting the lowest scoring rotamer or when more than one amino acid is manipulated simultaneously, selecting the lowest scoring rotamer combination;
  - iv. determining whether to accept or reject the mutation with the rotamer or rotamer combination selected in step (iii); and
  - v. assigning the amino acid residue or residues and their respective selected rotamer or rotamer combinations selected in step (iii) to said position/s and moving to another position along the

sequence;

said simulation steps are repeated until for each position along said sequence, the residue and residue's rotamer with the lowest energy score is selected, to obtain a virtually represented amino acid sequence with the lowest total energy score;

- f. expanding the reduced representation of the virtually represented amino acid sequence obtained in step (e) to its corresponding all-atom sequence representation thereby obtaining an amino acid sequence compatible with the predefined 3D structure[.];
- g. optionally, creating a computer output of the expanded all-atom representation of the primary structure/s obtained in step (f).

23  
32. (New) A means for practicing the method of claim 1, comprising:  
a computer based system for predicting at least one amino acid  
sequence compatible with a specified three-dimensional (3D)  
structure of a protein or peptide, said system comprising:

- a. input apparatus for specifying said 3D structure;
- b. a first memory for storing the specified 3D structure;
- c. a second memory having stored thereon an application program  
which when running, provides at least one amino acid sequence  
compatible with the specified 3D structure;

- d. a third memory for storing the at least one amino acid sequence obtained;
- e. a processor coupled to said input means, and to said first, second and third memories for representation of said amino acid sequence; and
- f. optionally, a display unit coupled to said processing means for displaying the amino acid sequence.

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Appendix B

Please amend claim 1 and add new claim 23 as outlined in the following "clean" copy of the claims.

1. A computer-implemented method for predicting at least one amino acid sequence compatible with a specified three-dimensional (3D) structure of a protein or peptide; which method comprises the steps of:
  - a. providing a coordinate set representing the backbone of said 3D structure;
  - b. constructing a reduced virtual representation for the 3D structure provide in step (a);
  - c. determining for each position along the virtual structure representation provided in step (b) its solvent accessibility;
  - d. constructing an initial amino acid sequence by randomly assigning for each position along the structure an amino acid residue selected randomly from a predefined group

of amino acids having a solvent accessibility compatible with the solvent accessibility of said position;

- e. randomly selecting one or more positions along the sequence provided in step (d) and applying on each position a Monte-Carlo simulation in sequence space and rotamer space, said simulation comprising one or more scoring function calculating steps which include:
  - i. randomly selecting one or more amino acid residues of the same solvent accessibility as that defined for said position to obtain a mutation;
  - ii. calculating an energy scoring function for each possible rotamer of each amino acid residue provided in step (i) based on their said reduced virtual representation;
  - iii. selecting the lowest scoring rotamer or when more than one amino acid is manipulated simultaneously, selecting the lowest scoring rotamer combination;
  - iv. determining whether to accept or reject the mutation with the rotamer or rotamer combination selected in step (iii); and
  - v. assigning the amino acid residue or residues and their respective selected rotamer or rotamer combinations selected in step (iii) to said position/s and moving to another position along the

sequence;

said simulation steps are repeated until for each position along said sequence, the residue and residue's rotamer with the lowest energy score is selected, to obtain a virtually represented amino acid sequence with the lowest total energy score;

- f. expanding the reduced representation of the virtually represented amino acid sequence obtained in step (e) to its corresponding all-atom sequence representation thereby obtaining an amino acid sequence compatible with the predefined 3D structure;
- g. optionally, creating a computer output of the expanded all-atom representation of the primary structure/s obtained in step (f).

*Rule 126* <sup>23</sup>  
~~32~~. A means for practicing the method of claim 1, comprising:  
a computer based system for predicting at least one amino acid sequence compatible with a specified three-dimensional (3D) structure of a protein or peptide, said system comprising:

- a. input apparatus for specifying said 3D structure;
- b. a first memory for storing the specified 3D structure;
- c. a second memory having stored thereon an application program which when running, provides at least one amino acid sequence compatible with the specified 3D structure;

- d. a third memory for storing the at least one amino acid sequence obtained;
- e. a processor coupled to said input means, and to said first, second and third memories for representation of said amino acid sequence; and
- f. optionally, a display unit coupled to said processing means for displaying the amino acid sequence.